

# Idiopathic giant cell myocarditis or cardiac sarcoidosis? A retrospective audit of a nationwide case series

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## Abstract

**Aims** Cardiac sarcoidosis (CS) and giant cell myocarditis (GCM) are inflammatory cardiomyopathies sharing histopathological and clinical features. Their differentiation is difficult and susceptible of confusion and apparent mistakes. The possibility that they represent different phenotypes of a single disease has been debated.

**Methods and results** We made a retrospective audit of 73 cases of GCM diagnosed in Finland since the late 1980s. All available histological material was reanalyzed as were other examinations pertinent to the distinction between GCM and CS. Finding granulomas in or outside the heart was considered diagnostic of CS and exclusive of GCM. Altogether 45 of the 73 cases of GCM (62%) were reclassified as CS. In all except one case, this was based on finding sarcoid granulomas that either had been originally missed ( $n = 29$ ) or misinterpreted ( $n = 11$ ) or were found in additional posttransplant myocardial specimens ( $n = 3$ ) or samples of extracardiac tissue ( $n = 1$ ) accrued over the disease course. Supporting the reclassification, patients relocated to the CS group had less heart failure at presentation (prevalence 20% vs. 46%,  $P = 0.017$ ) and better 1 year transplant-free survival (82% vs. 45%,  $P = 0.011$ ) than patients considered to represent true GCM.

**Conclusions** Recognizing granulomas in or outside the heart remains a challenge for the pathologist. Given that CS and GCM are considered distinct diseases and granulomas exclusive of GCM, many cases of GCM, if thoroughly scrutinized, may need reclassification as CS. However, whether CS and GCM are truly different entities or parts of a one-disease continuum has not yet been conclusively settled.

**Keywords** Cardiac sarcoidosis; Giant cell myocarditis; Differential diagnosis; Heart failure

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## Introduction

The first reports of giant cell myocarditis (GCM) and cardiac sarcoidosis (CS) date back to the early decades of the 20th century.<sup>1,2</sup> Still today, a hundred years later, clinicians remain puzzled by their many unknowns like what are their respective causes and mechanisms and are they genuinely different diseases or merely different segments of a single disease spectrum. Both conditions have been attributed to T lymphocyte-mediated autoimmune myocardial injury, and they have many similarities in myocardial histopathology and clinical manifestations.<sup>3–6</sup> The studies by Litovsky *et al.*<sup>4</sup> and Okura *et al.*<sup>6</sup> at the turn of millennium seemed, however,

to establish GCM and CS as different disease entities. Myocardial granulomas and fibrosis have since been taken as the histologic hallmarks of CS while prominent necrosis and a diffuse infiltrate of mixed inflammatory cells including multinuclear giant cells and eosinophils are considered peculiar for GCM.<sup>3,6–8</sup>

We have in Finland a registry of patients diagnosed during life with CS or GCM since the late 1980s.<sup>9</sup> Recently, additional cases diagnosed only at autopsy were identified and included from the cause-of-death registry. In reanalyzing the autopsy material, we found cases of CS mistaken for GCM.<sup>10</sup> In a parallel case, we came across an explanted heart showing abundant granulomas in a patient with a pretransplant diagnosis

of GCM. In response, we decided to audit each GCM diagnosis in our registry. To that end, we reassessed the original diagnostic slides and any later myocardial biopsies as well as samples of extracardiac tissue and other diagnostic studies. The need to consider reclassification of GCM was surprisingly high. Here, we detail the main causes for the apparent mistakes of CS for GCM but discuss also whether CS and GCM could represent a one-disease continuum rather than two different entities.

## Methods

### The cases

#### *Clinical registry*

The Myocardial Inflammatory Diseases in Finland (MIDFIN) study group is a cardiology research network maintaining a nationwide registry of adult patients diagnosed with CS or GCM since the late 1980s. The details of the registry are described in our earlier publications.<sup>9,11,12</sup> The data filed on individual patients include information about demographics, cardiac manifestations, and associated diseases as well as results of diagnostic imaging and laboratory studies and treatment with drugs and devices. All patients have been followed-up in the hospitals of the MIDFIN research network, and their outcome events including death, transplantation, and life-threatening arrhythmias have been recorded. The case was included as GCM in the registry if myocardial histology showed myocyte injury with or without necrosis associated with an inflammatory infiltrate variably composed of lymphocytes, histiocytes, eosinophils, and multinuclear GCs without other explanations. The presence of unequivocal non-necrotic granulomas was considered diagnostic of CS and exclusive of GCM. All diagnoses had been made by two cardiac pathologists one of whom (A.R.-S.) is also authoring the present work. At the end of 2015, the MIDFIN registry included 50 cases of idiopathic GCM fulfilling the above criteria. All except one of them could be included in the present work.

#### *Cause-of-death registry*

As described elsewhere,<sup>10</sup> we recently screened the Finnish cause-of-death registry to identify patients dying suddenly out of hospital and diagnosed with CS or GCM only at autopsy. The registry files were available to us in digital format from 1998 through 2015, and altogether, 820 605 death certificates were subjected to detailed screening.<sup>10</sup> In all, 24 candidate cases of GCM were identified based on the documentation of the primary cause of death as the ICD-10 codes I51.4 (myocarditis, unspecified) or I40 (acute myocarditis) with the phrase 'giant cell myocarditis' in the text body of the death certificate. The autopsies had been made by forensic (21/24) or general (3/24) pathologists.

### Methods of the audit

For the review of the 49 GCM cases from the MIDFIN registry, we acquired for microscopy all slides and histologic material still available from the original diagnostic myocardial biopsies as well as any specimens available from follow-up biopsies or explanted or autopsied hearts and any lifetime or autopsy samples of extracardiac tissues. In cases of difficult-to-assess myocardial histology, we made ancillary studies with immunohistochemistry using the following antibodies: CD3 (clone: 2VG6, Ventana, Phoenix, AZ), CD4 (clone: SP35, Cell Marque), CD8 (clone: 4B11, Novocastra), CD31 (clone: JC70A, Dako), CD68 (clone: PG-M1, Dako), and PD-L1 (clone: SP142, Abcam). In addition to microscopy, we also used other information pertinent to the differentiation of CS from GCM such as results of imaging studies with either 18-F-fluorodeoxyglucose positron emission tomography (<sup>18</sup>F-FDG PET) or computed tomography.

For the review of the 24 cases from the cause-of-death registry, the slides and histological material available from autopsies were re-examined. The written autopsy reports were scrutinized for observations of other cardiac diseases and extracardiac organ involvement. The lifetime medical records of the deceased were studied for their medical history and any cardiac symptoms and examinations shortly before death.

The histopathologic re-evaluation of all GCM cases was made by two pathologists (A.R.-S. and M.I.M.) with >10 years experience in cardiovascular pathology. Their consensus was needed to convert the diagnosis of GCM to CS in clinico-pathological meetings with the cardiologists (K.E., J.L., and M.K.).

### Criteria for reclassification of GCM

The histologic criteria for GCM were identical to the ones used previously with the addition that the presence of any myocardial granulomas recognizable with reasonable certainty, including the immature ones identified with help of immunohistochemistry, were considered diagnostic of CS. Furthermore, cases where histologic studies confirmed or <sup>18</sup>F-FDG PET strongly suggested the presence of extracardiac sarcoidosis were reclassified as CS even in the absence of myocardial granulomas.

### Ethical approvals

The MIDFIN registry study had the approval of the national ethical review board (STM/1219/2009). The National Authority for Medicolegal Affairs (4615/06.01.03.01/2016) and the National Institute for Health and Welfare (THL/691/5.05.00/2016) approved the study of cases from the

cause-of-death registry and the review of postmortem autopsy material. Our study complies with the Declaration of Helsinki, and written informed consent was obtained from each patient alive at the time of recruitment into the MIDFIN registry study.

## Statistical analysis

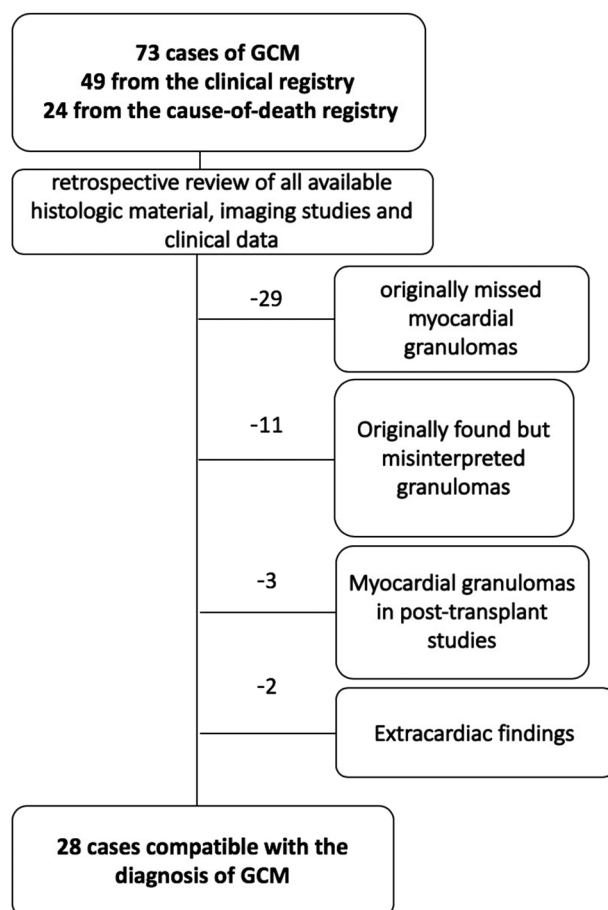
Statistical analysis was used to compare the cases of GCM reclassified as CS with the ones maintaining the original diagnosis. Baseline characteristics are presented as mean  $\pm$  standard deviation or as median (interquartile range) for continuous variables and as frequencies for categorical variables. Group comparisons were made using Student's *t*-test, Mann–Whitney *U* test, or  $\chi^2$  statistic as appropriate. In survival analysis, follow-up was calculated from the date of

first medical contact because of symptoms that led to the diagnosis of GCM during life or were attributable to GCM in cases diagnosed at autopsy. Survival analysis was carried out by the Kaplan–Meier method with the composite of death from any cause or cardiac transplantation as the outcome endpoint. Cox regression analysis was used to adjust for confounding factors when comparing event-free survival between the diagnostic groups. *P* values  $<0.05$  were considered statistically significant. Analyses were performed using SPSS–24 for Macintosh (SPSS Inc, IL) and Xlstat Lifesciences (Addinsoft, Paris, France).

## Results

### The rate and causes of reclassification of giant cell myocarditis

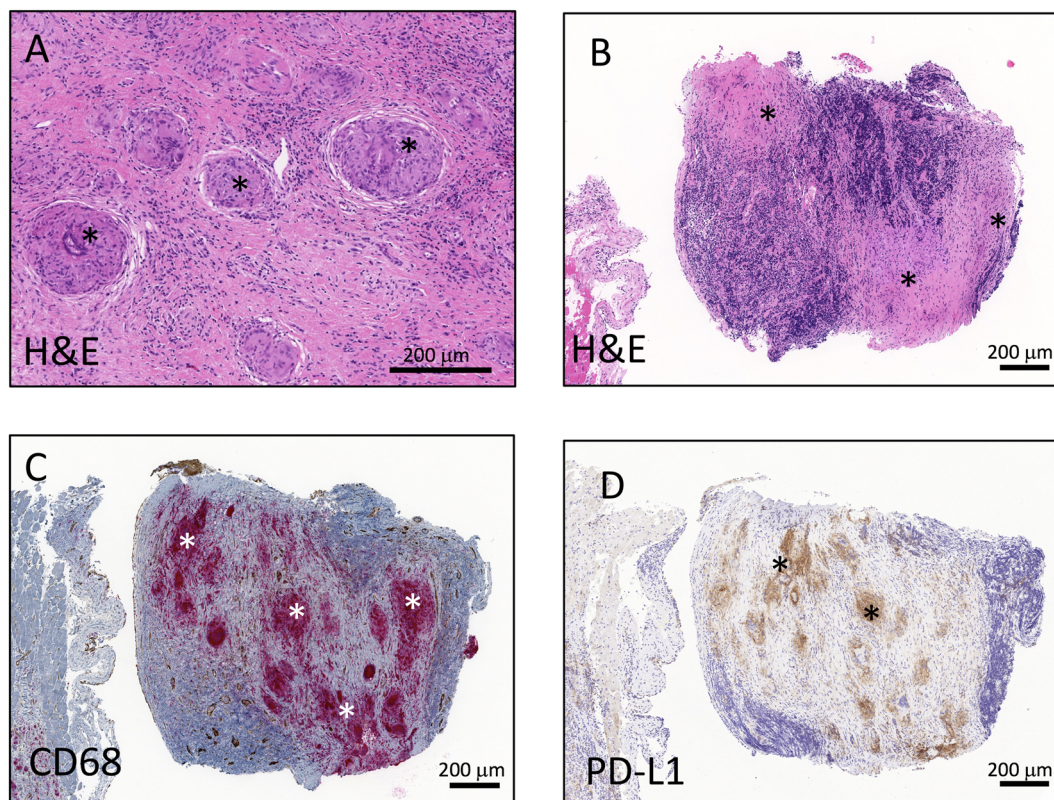
**Figure 1** Flow chart summarizing the study material and the reasons for reclassification of GCM as CS. Of the 24 cause-of-death registry cases, 10 were reclassified because of originally found but misinterpreted granulomas and nine for myocardial granulomas missed at autopsy. All remaining reasons pertain to cases from the MIDFIN registry.



After re-evaluation of the individual GCM diagnoses, 26 out of the 49 cases in the MIDFIN registry were reclassified as CS as were 19 of the 24 cases filed as GCM in the cause-of-death registry. The main reasons for reclassification are summarized in *Figure 1*. In 20 cases from the MIDFIN registry and nine cases from the cause-of-death registry, re-evaluation exposed originally missed myocardial granulomas varying from occasional well-formed follicular structures to immature granulomas in different stages of development. With the help of immunohistochemistry, the immature granulomas were recognized more confidently. *Figure 2* exemplifies a well-formed granuloma (*Figure 2A*) and an immature one first in haematoxylin and eosin (H&E) staining (*Figure 2B*) and after immunostaining for CD68 (*Figure 2C*) and PD-L1 (*Figure 2D*). Even staining for CD4 positive T helper cells was of some help whereas CD3 and CD8 positive T cells were scattered around the myocardium and did not highlight the granulomas. Recognition of GCs and granulomas in the postmortem myocardium was complicated by frequent tissue autolysis (*Figure 3A*). In altogether 11 cases, 10 from the cause-of-death registry and one from the MIDFIN registry, presence of extracardiac, and even cardiac granulomas had been correctly recognized and reported at the autopsy, but the diagnosis assigned by the forensic or general pathologist was GCM. The most common sites for the extracardiac granulomas were mediastinal lymph nodes, lungs, kidneys, and liver (*Figure 3B–D*). In two cases transplanted for GCM, re-evaluation of specimens available from the native hearts revealed granulomas missed in the original explant study. In one further posttransplant case, follow-up allograft biopsies showed recurrence of disease with myocardial granulomas diagnostic of CS. Finally, extracardiac findings were the reason for reclassification in two instances. In one of them, sarcoid granulomas were found on microscopy of renal tissue samples while in the other case, with poor-quality original



**Figure 2** (A) Well-formed granulomas (asterix) in the fibrotic cardiac tissue from a CS patient (H&E-staining, original magnification  $\times 25$ ). (B) Endomyocardial biopsy showing dense lymphocytic infiltrate with pale areas representing immature granulomas (asterix, H&E-staining, original magnification  $\times 10$ ). Immunohistochemical staining for markers of CD68 (macrophages, red) and CD31 (endothelium, brown) (Panel C) and PD-L1 (Panel D) highlights the granulomas.



myocardial slides,  $^{18}\text{F}$ FDG PET taken at presentation showed extracardiac inflammatory activity (mediastinal lymph nodes, lungs) favouring the diagnosis of CS. Altogether 32 of the 45 reclassified cases had isolated CS, that is, no signs of extracardiac sarcoid granulomas had been recorded either at autopsy or in whole-body  $^{18}\text{F}$ FDG PET.

### Comparison between the groups of cardiac sarcoidosis and giant cell myocarditis resulting from re-evaluation

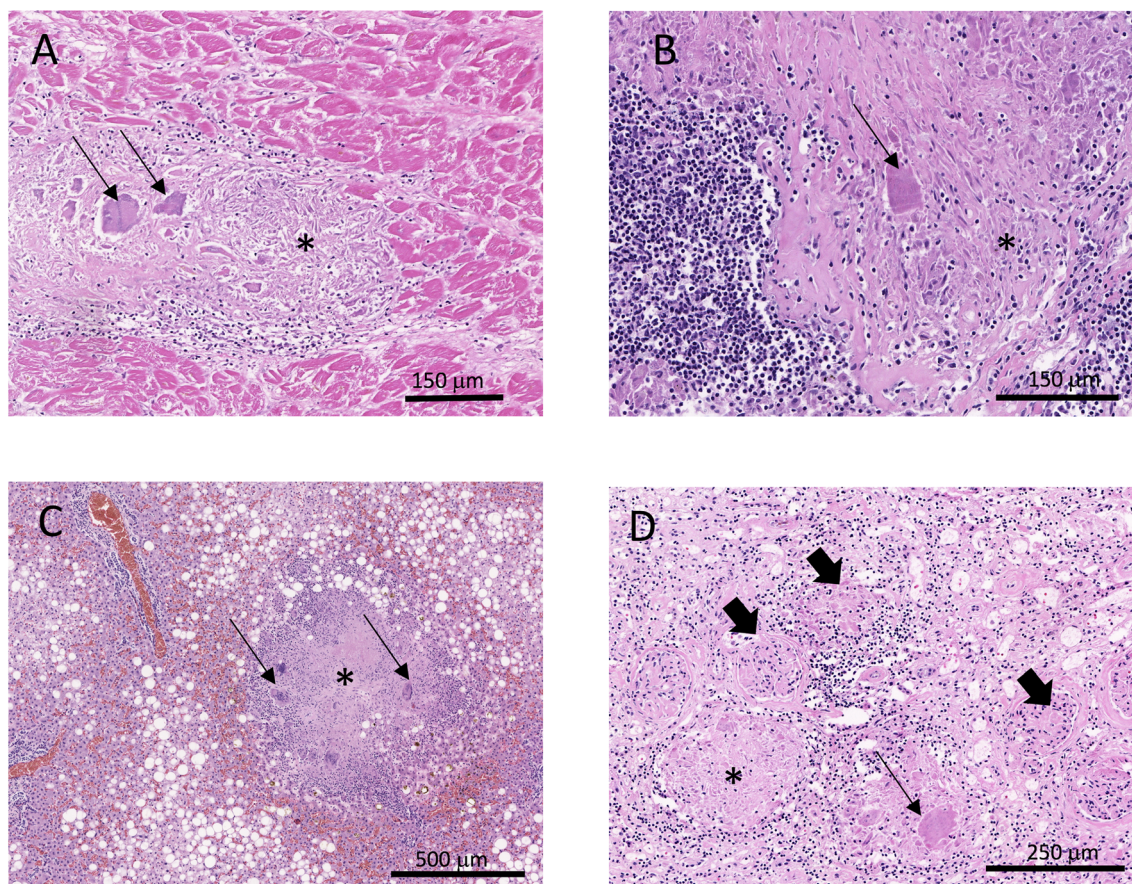
Table 1 compares patients' characteristics, treatment, and cardiac events between the subgroups of GCM reclassified as CS and keeping the GCM diagnosis. At presentation, patients relocated to the CS group were younger, had lower circulating troponin-T and NT-proBNP and were less likely to have heart failure. As Table 1 shows, altogether 16 patients reclassified as CS had received GCM-targeted immunosuppression including cyclosporine. Impaired renal function (glomerular filtration rate  $< 60 \text{ mL/min/m}^2$ ) was observed during

follow-up in six of them with severe renal failure (glomerular filtration rate  $< 30 \text{ mL/m}^2/\text{min}$ ) being noted in one case. No malignancies were observed during follow-up, but one case of recurrent diverticulitis was considered an infectious complication of immunosuppression. In 2019, immunosuppression for GCM was fully withdrawn in five stable patients reclassified as CS; no signs of disease relapse have been noted in any of them over a minimum of 6 months of follow-up.

Figure 4 shows the transplant-free survival graphs for the GCM patients reclassified as CS ( $n = 34$ ) and maintaining the GCM diagnosis ( $n = 25$ ); cases with sudden death as the only presenting manifestation ( $n = 14$ ) were excluded from the analysis. The Kaplan–Meier estimate (95% confidence interval) of 1 year transplant-free survival was 82% (70–95%) in CS and 45% (24–66%) in GCM. At 5 years, the estimate was 46% (28–64%) in CS and 27% (7–47%) in GCM. In a Cox regression analysis with diagnosis, age, and presentation with heart failure as explanatory factors, CS was an independent predictor of outcome with a hazard ratio (95% confidence interval) of 0.370 (0.169–0.809,  $P = 0.013$ ).



**Figure 3** Autopsy samples of myocardium (Panel A, H&E staining, original magnification  $\times 20$ ) and lymph node from the same patient (Panel B, H&E staining, original magnification  $\times 40$ ) demonstrate the difficulties in postmortem studies. Tissue autolysis makes the diagnostic microscopy more challenging as the GCs (thin arrows) loose nuclei and granulomas (asterix) become less evident. Extracardial granulomas (asterix) seen in the liver (Panel C, H&E staining, original magnification  $\times 10$ ) and in kidney (Panel D, asterix, H&E staining, original magnification  $\times 20$ ). These can even be confused with normal autolytic glomeruli of the kidney (Panel D, thick arrows).



## Discussion

The present study, an audit of the cases of GCM diagnosed in Finland since the late 1980s, was our response to seeing in a short while several cases of GCM raising suspicion of misdiagnosed CS. We found that the original GCM diagnoses appeared to need conversion to CS in more than 60% of cases, mainly because of the identification of myocardial granulomas that had originally escaped detection or looked too equivocal to meet the criteria at that time. In support of our reclassification, patients relocated to the CS group had less severe myocardial injury and less heart failure at presentation than those keeping the GCM diagnosis. They also had moderately better transplant-free survival. Importantly, the present work was designed on the premise of CS and GCM being distinct disease entities. In the end, however, our findings combined with the earlier literature set us doubting that concept and reviving the possibility that CS

and GCM instead may represent different degrees of severity of a single disease.

### Role of myocardial granulomas in the reclassification of GCM

The conspicuously high rate of diagnostic reclassifications because of previously 'missed' myocardial granulomas calls for explanations. Non-necrotizing myocardial granulomas, observable as tightly packed and well-demarcated follicular aggregates of epithelioid macrophages, lymphocytes, and multinuclear GCs, are the histologic hallmark of CS.<sup>13–15</sup> They are thought to trap the causative agents and limit the local inflammatory injury.<sup>13</sup> Immature granulomas, representing an earlier stage of development, are looser and less well-demarcated assemblies of immune cells that may escape detection on routine microscopy.<sup>14,15</sup> In the present work,

**Table 1** Patient characteristics and follow-up information by the reclassified groups

	CS (N = 45)	GCM (N = 28)	P value
Age at presentation, year	49 ± 13	58 ± 10	0.003
Female sex, n	32 (71)	19 (68)	0.768
Main presenting manifestation, n			
High grade AVB	15 (33)	6 (21)	0.275
Heart failure	9 (20)	13 (46)	0.017
Sustained VT	4 (9)	2 (7)	0.580
Aborted SCD <sup>a</sup>	1 (2)	1 (4)	1.000
SCD	11 (24)	3 (11)	0.147
Other	5 (11)	3 (11)	0.637
LVEF at presentation, % <sup>b</sup>	44 ± 15	38 ± 15	0.139
Cardiac troponin T, ng/L <sup>c</sup>	50 (18–61)	1239 (759–2522)	<0.001
NT-proBNP, ng/L <sup>d</sup>	1710 (985–4611)	5273 (2782–11309)	0.007
<i>Essentials of treatment and outcome events in cases with lifetime disease presentation</i>			
	N = 34	N = 25	
Implantable cardioverter defibrillator, n	1+7 (50)	13 (52)	0.412
Triple drug immunosuppression, n <sup>e</sup>	16 (47)	14 (56)	0.529
Years of follow-up, median (range)	2.3 (1.1–6.5)	0.5 (0.1–1.6)	<0.001
Deaths, n	13 (38)	5 (20)	
Heart transplantations, n	7 (21) <sup>f</sup>	11 (44) <sup>g</sup>	

Data are expressed as mean ± standard deviation, number (%) of cases, or median (interquartile range)

AVB, atrioventricular block; CS, cardiac sarcoidosis; GCM, giant cell myocarditis; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B type natriuretic peptide; SCD, sudden cardiac death; VT, ventricular tachycardia.

<sup>a</sup>Cardiac arrest with successful resuscitation.

<sup>b</sup>Data available in 55 cases.

<sup>c</sup>Data available in 44 cases.

<sup>d</sup>Data available in 43 cases.

<sup>e</sup>Combination consisting of prednisolone, azathioprine, and cyclosporine.

<sup>f</sup>One patient died post-transplantation.

<sup>g</sup>Three patients died post-transplantation.

finding myocardial granulomas, whether well-formed or immature-looking, was an indication to reclassify GCM as CS. In the original diagnostic studies of our clinical case series, only unequivocal follicular granulomas were considered diagnostic of CS.<sup>11,12</sup> Thus, evolving diagnostic criteria constitute one explanation for the high rate of reclassifications. Another explanation is the use of ancillary immunohistochemistry that helped us detect immature granulomas. The third explanation comes from the autopsy series in which even fully formed myocardial granulomas had escaped detection. Because of the rarity of CS and GCM forensic and general pathologists encounter them too seldom to gain the experience needed for their proper recognition and differentiation. GCs and granulomas also lose their nuclear structure in the early stage of autolysis which complicates their identification in postmortem examinations.

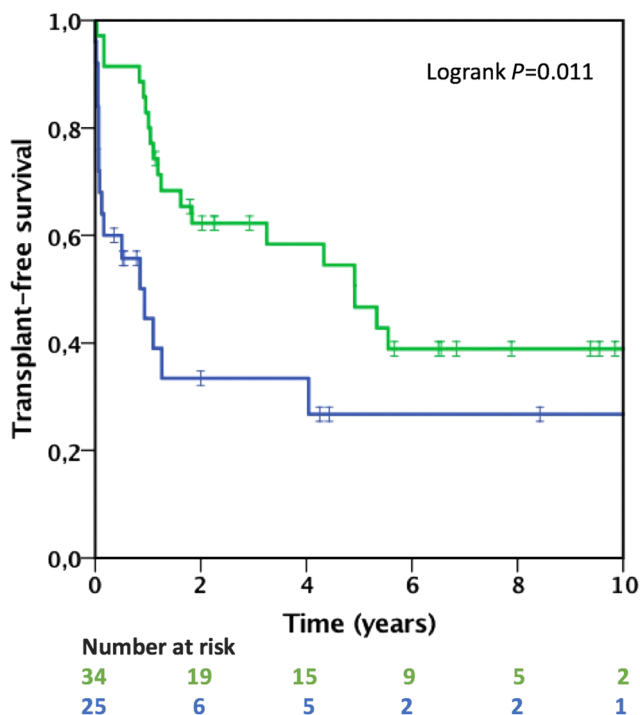
A crucial point in our analyses is the categorical interpretation of myocardial granulomas as exclusive of the diagnosis of GCM. Admittedly, this is an issue short of unanimity among researchers. Like us here, Davies *et al.*<sup>8</sup> and Litovsky *et al.*<sup>4</sup> have emphasized the absence of granulomas in GCM, and this view was adopted also in the landmark report by the Multicenter GCM Study Group in 1997.<sup>7</sup> Yet in the subsequent work of the same group,<sup>6</sup> comparing CS and GCM, presence of myocardial granulomas was not considered exclusive of the diagnosis of GCM. Cooper and ElAmm<sup>16</sup> have also indicated that poorly formed myocardial granulomas can be seen in GCM. This variation in the diagnostic

interpretation of granulomas clouds the distinction between CS and GCM and complicates the comparison of findings from different studies. It may also explain why, in our series, forensic and general pathologists had frequently diagnosed GCM even when recognizing granulomas in or outside the heart. Ultimately, it mirrors the question of whether we are dealing here with one or two disease entities.

## Other causes for reclassification

In a small number of cases reclassification of GCM as CS was based on the presence of extracardiac findings indicative of sarcoidosis. We think today that patients with an apparently typical histology of GCM but non-fulminant clinical picture should undergo whole-body<sup>17</sup>F-FDG PET to identify targets for additional diagnostic biopsies. Exposing extracardiac sarcoid granulomas could save the patient from overaggressive treatment. In two cases of GCM, a thorough re-evaluation of the specimens still available from explanted hearts revealed granulomas diagnostic of CS. This taught us that not only endomyocardial biopsies but also explant studies are susceptible of sampling errors because of the sparsity of granulomas in burnt-out native hearts. In endomyocardial biopsies, the bioptome may not hit the area of inflammation or misses granulomas even when showing the presence of myocarditis. Any granulomas residing deeper in the myocardium are out of the reach of the bioptome.

**Figure 4** Kaplan–Meier graphs for transplant-free survival from onset of symptoms. The blue line stands for patients keeping the GCM diagnosis at re-evaluation, the green line representing patients reclassified as CS. Cases without any lifetime symptoms and follow-up, that is, presenting with unexpected sudden cardiac death ( $n = 14$ ), were excluded from the analysis.



### Are cardiac sarcoidosis and giant cell myocarditis different diseases or different segments of a single disease spectrum?

At the turn of the millennium, two research groups<sup>4,6</sup> reported on comparisons between cases of CS and GCM. Litovsky *et al.*<sup>4</sup> analysed in retrospect myocardial autopsy specimens available from eight patients with GCM and seven patients with CS. The main microscopic discriminators were granulomas, being fully absent in GCM, and myocyte necrosis, which was not seen in CS. Okura *et al.*,<sup>6</sup> in turn, compared cardiac histopathology and clinical characteristics between 73 cases of GCM and 42 cases of CS collected from 48 centres worldwide. Although all centres contributed cases of GCM, the majority, surprisingly, did not have a single case of CS. There was also a marked racial mismatch between the groups. In contrast to Litovsky *et al.*,<sup>4</sup> Okura *et al.*<sup>6</sup> reported that myocardial necrosis and granulomas were present in both CS and GCM although necrosis was more extensive in GCM while granulomas were more common in CS. Eosinophils and lymphocytes were found in higher numbers in GCM whereas there was more myocardial fibrosis in CS. The GCM group had more heart failure at presentation and a

shorter transplant-free survival during follow-up. Although these works<sup>4,6</sup> have been widely cited as establishing the concept of CS and GCM being two unique diseases, both fall short of constituting firm scientific evidence thereof.

CS and GCM share many features that counter the argument for fully different diseases. First, T lymphocyte-mediated inflammation appears crucial in both<sup>3–5</sup> and either condition has an association with thymic tumours.<sup>3,8,17–19</sup> Second, their end-to-end spectrum of cardiac manifestations is equal, and although rapidly progressive heart failure is much more common in GCM,<sup>3,6</sup> CS can also cause fulminant heart failure<sup>20–22</sup> while a protracted clinical course, in turn, is possible in GCM.<sup>23,24</sup> Third, clinically and histopathologically typical GCM can coexist with proven extracardiac sarcoidosis.<sup>8,25,26</sup> In the 1950s, Tesluk<sup>27</sup> described idiopathic GCM as a condition commonly associated with granulomas outside the heart, and half a century later, Cooper wrote that 5–10% of his patients with GCM have granulomas in lymph nodes and liver.<sup>3</sup> In their autopsy study and review of CS, Roberts *et al.*<sup>28</sup> concluded that the cases of GCM with granulomas outside the heart represent CS and that it may not be possible to distinguish these conditions by histologic examination of the heart alone. All in all, the present findings together with a careful analysis of the earlier literature set us to question the concept of two unique and different diseases. We think today that CS and GCM more likely either are intimately related types, ‘twins’, of T cell myocarditis or represent different degrees of severity of a single underlying disease.

### Limitations

The main limitation of our work is that the results are specific to the applied diagnostic criteria. In re-evaluating cases of GCM, we ignored the clinical case history and focused only on histopathology. To be precise, recognizing granulomas in or outside the heart set us to reclassify the case as CS. Had we used other criteria, like the ones of Okura *et al.*<sup>6</sup> whereby myocardial granulomas do not exclude GCM if the degree of necrosis is out of proportion of the degree of granulomatous inflammation, the results would likely have been different. Yet it is unknown how ‘out of proportion’ should be defined in this context. Subjectivity is an unavoidable limitation of microscopy. It may be the more relevant the smaller histopathologic nuances, like immature granulomas here, are under scrutiny. We tried to minimize this limitation by relying on the consensus of two experienced cardiac pathologists working both independently and in simultaneous microscopy sessions. Although the reclassifications were made by histopathology, the investigators were not blinded to the clinical data. This is a limitation of the analyses comparing the



characteristics and outcomes of the groups arising from the re-evaluation.

to settle the issue of two unique entities versus one disease with varying faces.

## Clinical implications and concluding remarks

It seems sensible to give up any sharp dichotomy of CS and GCM in clinical work. Whenever one is suspected, additional examinations are warranted to expose disease outside the heart, and the patients should be monitored for signs of extracardiac involvement during follow-up. Irrespective of their diagnostic interpretation, myocardial granulomas, and their recognition, remain important because their presence implicates better prognosis. To avoid missing granulomas, thorough microscopy of all available tissue samples is needed, and the use of immunochemistry may help. More basic and clinical research is needed to unravel the causes and mechanisms of CS and GCM and to lay the evidence base for their proper treatment. Such studies can also be expected

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## Conflict of interest

None declared.

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## References

1. Saltykow S. Über diffuse myokarditis. *Virchows Archiv für Pathologische Anatomie* 1905; **182**: 1–39.
2. Bernstein M, Konzelmann F, Sidlick D. Boeck's sarcoid: report of a case with visceral involvement. *Ann Intern Med* 1929; **44**: 721–734.
3. Blauwet LA, Cooper LT. Idiopathic giant cell myocarditis and cardiac sarcoidosis. *Heart Fail Rev* 2013; **18**: 733–746.
4. Litovsky SH, Burke AP, Virmani R. Giant cell myocarditis: an entity distinct from sarcoidosis characterized by multiphasic myocyte destruction by cytotoxic T cells and histiocytic giant cells. *Mod Pathol* 1996; **9**: 1126–1134.
5. Kittleson MM, Minhas KM, Irizarry RA, Ye SQ, Edness G, Breton E, Conte JV, Tomaselli G, Garcia JGN, Hare JM. Gene expression in giant cell myocarditis: altered expression of immune response genes. *Int J Cardiol* 2005; **102**: 333–340.
6. Okura Y, Dec GW, Hare JM, Kodama M, Berry GJ, Tazelaar HD, Bailey KR, Cooper LT. A clinical and histopathologic comparison of cardiac sarcoidosis and idiopathic giant cell myocarditis. *J Am Coll Cardiol* 2003; **41**: 322–329.
7. Cooper LT Jr, Berry GJ, Shabetai R. Idiopathic giant-cell myocarditis—natural history and treatment. Multicenter Giant Cell Myocarditis Study Group Investigators. *N Engl J Med* 1997; **336**: 1860–1866.
8. Davies MJ, Pomerance A, Teare RD. Idiopathic giant cell myocarditis—a distinctive clinico-pathological entity. *Br Heart J* 1975; **37**: 192–198.
9. Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, Ylitalo K, Kaikkonen K, Tuohinen S, Haataja P, Kerola T, Kokkonen J, Pelkonen M, Pietilä-Effati P, Utriainen S, Kupari M. Cardiac sarcoidosis: epidemiology, characteristics and outcome over 25 years in a nationwide study. *Circulation* 2015; **131**: 624–632.
10. Ekström K, Lehtonen J, Nordenswan H-K, Mäyränpää MI, Sokolowski-Räisänen A, Kandolin R, Simonen P, Pietilä-Effati P, Alatalo A, Utriainen S, Rissanen TT, Haataja P, Kokkonen J, Vihinen T, Miettinen H, Kaikkonen K, Kerola T, Kupari M. Sudden death in cardiac sarcoidosis: an analysis of clinical and cause-of-death registries. *Eur Heart J* 2019; **40**: 3121–3128.
11. Ekström Kandolin R, Lehtonen J, Salmenkivi K, Räisänen-Sokolowski A, Lommi J, Kupari M. Diagnosis, treatment, and outcome of giant-cell myocarditis in the era of combined immunosuppression. *Circ Heart Fail* 2013; **6**: 15–22.
12. Ekström K, Lehtonen J, Kandolin R, Räisänen-Sokolowski A, Salmenkivi K, Kupari M. Long-term outcome and its predictors in giant cell myocarditis. *Eur J Heart Fail* 2016; **18**: 452–458.
13. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Müller-Quernheim J. Sarcoidosis. *Lancet* 2014; **383**: 1155–1167.
14. Lagana SM, Parvani AV, Nichols LC. Cardiac sarcoidosis. A pathology-focused review. *Arch Pathol Lab Med* 2010; **134**: 1039–1046.
15. Serei WD, Fyfe B. The many facies of cardiac sarcoidosis. *Am J Clin Pathol* 2019 Nov 26. pii: aqz169 [Epub ahead of print]; **153**: 294–302.
16. Cooper LT, ElAmm C. Giant cell myocarditis. Diagnosis and treatment. *Herz* 2012; **37**: 632–636.
17. Hato T, Yamaguchi M, Sugiyama A, Aoki K, Inoue Y, Fukuda H, Gika M, Higashi M, Nakayama M. “Hatched egg” of thymoma with sarcoidosis. *World J Surg Oncol* 2019; **17**: 151.
18. Holbro A, Jauch A, Lardinois D, Tzankov A, Dirnhofer S, Hess C. High prevalence of infections and autoimmunity in patients with thymoma. *Hum Immunol* 2012; **73**: 287–290.
19. Gadalla SM, Rajan A, Pfeiffer R, Kristinsson SY, Björkholm M, Landgren O, Giaccone G. A population-based assessment of mortality and morbidity patterns among patients with thymoma. *Int J Cancer* 2011; **28**: 2688–2694.
20. Stewart RE, Graham DM, Godfrey GW, Friedeman HZ, Das SK, Shea MJ. Rapidly progressive heart failure resulting from cardiac sarcoidosis. *Am Heart J* 1988; **115**: 324–326.
21. Varian K, Xu WD, Lin W, Unai S, Tong MZ, Soltesz E, Krishnaswamy A, Kapadia S, Feitell S, Hanna M, Joyce E, Schoenhagen P, Starling RC, Taylor DO, Perez AL. Minimally invasive

- biventricular mechanical circulatory support with Impella pumps as a bridge to heart transplantation: a first-in-the-world case report. *ESC Heart Fail* 2019; **6**: 552–554.
22. Ammirati E, Veronese G, Brambatti M, Merlo M, Cipriani M, Potena L, Sormani P, Aoki T, Sugimura K, Sawamura A, Okumura T, Pinney S, Hong K, Shah P, Braun O, Van de Heyning CM, Montero S, Petrella D, Huang F, Schmidt M, Raineri C, Lala A, Varrenti M, Foà A, Leone O, Gentile P, Artico J, Agostini V, Patel R, Garascia A, Van Craenenbroeck EM, Hirose K, Isotani A, Murohara T, Arita Y, Sionis A, Fabris E, Hashem S, Garcia-Hernando V, Oliva F, Greenberg B, Shimokawa H, Sinagra G, Adler ED, Frigerio M, Camici PG. Fulminant versus acute nonfulminant myocarditis in patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 2019; **74**: 299–311.
  23. Ren H, Poston RS Jr, Hruban RH, Baumgartner WA, Baughman KL, Hutchins GM. Long survival with giant cell myocarditis. *Mod Pathol* 1993; **6**: 402–407.
  24. Maleszewski JJ, Orellana VM, Hodge DO, Kuhl U, Schultheiss HP, Cooper LT. Long-term risk of recurrence, morbidity and mortality in giant cell myocarditis. *Am J Cardiol* 2015; **115**: 1733–1738.
  25. Davidoff R, Palacios I, Southern J, Fallon JT, Newell J, Dec GW. Giant cell versus lymphocytic myocarditis: a comparison of their clinical features and long term outcome. *Circulation* 1991; **83**: 953–961.
  26. Nakasuka K, Ito S, Miyata K, Inomata M, Yoshida T, Tamai N, Suzuki S, Murakami Y, Sato K, Suzuki S, Eishi Y, Morimoto S-I. A case of idiopathic giant cell myocarditis with a past history of sarcoidosis. *J Cardiol Cases* 2013; **13**: 35–39.
  27. Tesluk H. Giant cell versus granulomatous myocarditis. *Am J Clin Pathol* 1956; **26**: 1326–1330.
  28. Roberts W, McAllister H, Ferrans V. Sarcoidosis of the heart: a clinicopathologic study of 35 necropsy patients (group I) and review of 78 previously described necropsy patients (group II). *Am J Med* 1977; **63**: 86–108.